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REMARKS

Section 112, first paragraph

Claims 27-29, 34 and 60 are rejected under 35 USC Section 112, first paragraph as failing to comply with the written description requirement. The basis for this rejection is that the amendment to claims 27, 34 and 60 introduces new matter into the specification because the specification allegedly "only provides support for contemplation of methods where the antibody to be used in the claimed methods blocks ligand activation of an ErbB receptor *substantially* more effectively than monoclonal antibody 4D5."

Applicants have amended claims 27, 34 and 60 to include the term "substantially," thereby obviating the Examiner's first basis for rejecting these claims.

The Examiner further urges that the claimed inventions lack written description in view of the term "monoclonal antibody 4D5." The Examiner urges that in view of the definition of the 4D5 antibody, it appears that the claimed methods comprise the use of an antibody that may be functionally compared to an antibody that has very little in common with the antibody that was used in the working examples (Trastuzumab, huMAb 4D5-8).

In order to obviate this basis of the rejection, claims 27, 34 and 60 have been amended herein by replacement of the expression "monoclonal antibody 4D5" with "humanized monoclonal antibody huMAb4D5-8," thus obviating the second basis of the rejection.

Reconsideration and withdrawal of the Section 112 rejection of claims 27-29, 34 and 60 is respectfully requested.

Claims 1, 2, 4-9, 12, 13, 16-22, 24-26, 61, 62 and 63 are rejected under 35 USC Section 112, first paragraph as failing to comply with the written description requirement.

The Examiner explains that the basis for this rejection is that the specification allegedly lacks written description of "monoclonal antibody 2C4" and "monoclonal antibody 4D5" The Examiner urges that the term monoclonal antibody 2C4 without the reference ATCC number appears to refer to almost any

antibody that might bind to Her-2.

In order to obviate this basis of the rejection, claims 1, 16-17, and 61-63 have been amended to cross reference the ATCC deposit number for MAb 2C4.

Reconsideration and withdrawal of the Section 112 rejection of claims 1, 2, 4-9, 12, 13, 16-22, 24-26, 61, 62 and 63 is respectfully requested.

Section 102(e)

Claims 1, 2, 7, 12, 13, 16, 17 and 20 are rejected under 35 USC Section 102(e) as being anticipated by Greene *et al.* (US Patent No. 5,024,311), as evidenced by Jardines *et al. Pathobiology* 61:268-282 (1993).

The Examiner urges that the rejection is maintained and applied newly to claims 16 and 17, because, in the Examiner's view, antibodies may block binding of monoclonal antibody 2C4 by binding to the epitope that 2C4 binds to or by acting on the antigen to make the epitope disappear; that the preferred antibody in Greene is 7.16.4, "which is an antibody that binds to a similar epitope on Her-2 that monoclonal antibody 4D5 binds to"; that 4D5 causes internalization of ErbB2; and that "absent evidence to the contrary the Greene antibody is one which would block binding of monoclonal antibody 2C4."

This basis of the rejection is obviated by the amendment of claim 1 to recite that the antibody "cross-blocks" binding of monoclonal antibody 2C4 to ErbB2. See page 15, line 21 for support for this amendment. Since MAb 4D5, upon which the Examiner's reasoning for rejecting the claims is premised, does not cross-block binding of 2C4 to HER2 (Table 1 on page 1555 of Fendly *et al. Cancer Research* 50:1550-1559 (1990), of record), Applicants believe this basis of the rejection is obviated.

The Examiner further urges that because the phrase monoclonal antibody 2C4 is so broad as to encompass any antibody that may happen to contain a residue in common with residues derived from the murine monoclonal antibody ATCC HB-12697, the phrase blocking binding of monoclonal antibody 2C4 may refer to blocking of almost any antibody.

This basis of the rejection is obviated by the amendment of claim 1 to

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reference the ATCC deposit number for MAb 2C4.

Reconsideration and withdrawal of the Section 102 rejection is respectfully requested in view of the above.

Section 103

Claims 1, 2, 4, 7, 16, 17, 20, 24-26, 28, 29, 34 and 60-63 are rejected under 35 USC Section 103(a) as being unpatentable over Hudziak *et al.* (US Patent 5,725,856) and Jardines *et al.*, in view of Sliwkowski *et al. J. Biol. Chem* 269: 14661-14665 (1994), or Klapper *et al. Oncogene* 14: 2099-2109 (1997), and further in view of Plowman (US Patent No. 5,804,396) or Greene (US Patent No. 6,417,168).

Claims 1, 18, 19 and 21 are rejected under 35 USC Section 103 as being unpatentable over Hudziak *et al.* and Jardines *et al.* in view of Sliwkowski *et al.* or Klapper *et al.*, and further in view of Plowman *et al.* or Greene *et al.* and further in view of Grim *et al.*, *Am. J. Respir. Cell Mol. Biol.* 15:348-354 (1996).

The Examiner urges that Hudziak *et al.* teaches methods of inhibiting the growth of tumor cells by administering to a patient antibodies capable of inhibiting HER2 (ErbB2) function, and teaches methods of inhibiting the growth of tumor cells that overexpress a growth factor receptor, but "is silent on the question of treating a subgroup of patients that express both EGFR and ErbB2." Jardines is cited for teaching the patients with breast cancer who coexpress EGFR and ErbB2 had the shortest survival time of all the different subgroups of patients. The Examiner urges that "Jardines teaches that such a subgroup of patients is known to exist and, because of their shorter survival time, teaches a motivation to treat such patients." The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art that the time the invention was made to have used ErbB2 antibodies that inhibited the function of ErbB2 for the treatment of cancers that express both EGFR and ErbB2.

The Examiner status that the combination of Hudziak and Jardines "teaches generally methods for the treatment of cancers expressing both EGFR and ErbB2, comprising the use of antibodies that bind to ErbB2, and Hudziak contemplates

antibodies that bind to ErbB2 and inhibit ligand binding to an ErbB growth factor receptor, or the down regulation of the growth factor, the combination of Hudziak and Jardines fail to specifically teach methods comprising the use of antibodies that inhibit the formation of an ErbB hetero-oligomer." The Examiner further contends that such antibodies are known in the art, as evidenced the teachings of Sliwkowski that MAb 2C4 inhibits activation of ErbB2 by heregulin and Klapper that purportedly teaches antibodies that bind to ErbB2 and inhibit interaction of ErbB2 with other ErbB receptors. The Examiner additionally urges that the prior art as evidenced by Plowman, Akita and Greene, recognized that the inhibition of ErbB2 oligomerization with other ErbB receptors is a therapeutic target for the treatment of cancer, that Plowman teaches therapeutic agents that inhibit signal transduction by HER2 heterodimers, that Greene teaches methods for treatment of cancer comprising administering a peptide that inhibits the formation of ErbB protein dimers, where the dimers may be heterodimers.

The Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have used the antibodies of either Sliwkowski or Klapper in the method of Hudziak for the treatment of cancers that express both EGFR and ErbB2, that one would have been motivated to use antibodies that inhibited ligand activation of an ErbB receptor in view of the fact that the art recognized that ErbB2 was activated by the formation of heterodimers and that ErbB2 activation plays a role in the growth of cancer cells.

As to "dosing" claims 24-26, the Examiner states that it would have been *prima facie* obvious to one of ordinary skill in the art to have modified the methods of Hudziak to include such treatment regimens.

With respect to claims 18-19 and 21 concerning therapy with an antibody fragment (claim 18), such as a Fab (claim 19), which is not conjugated with a cytotoxic agent in claim 21, the Examiner relies on Grim *et al.* as allegedly teaching that the ErbB2 receptor is a therapeutic target in lung cancer and that antibody fragments can be used for therapeutic purposes.

Applicants submit that the presently claimed invention is patentable over the

cited art.

In the examples of the Hudziak patent (cols. 13-19), the breast tumor cells treated with the antibodies were selected based on HER2 overexpression, rather than expression of EGFR. While EGFR is described, it is intended to be targeted with an antibody that binds to EGFR, rather than one which binds to HER2 (see, *e.g.*, col. 3, lines 1-12; col. 5, lines 20-67; col. 6, lines 14-30). Therapy of EGFR-expressing cancer with an antibody that targets a different antigen, namely HER2, is counterintuitive.

Applicants submit that therapy of a cancer that expresses EGFR with a HER2 antibody is nonobvious over the art.

The preferred antibody in Hudziak *et al.*, the 4D5 antibody, is specifically excluded by the claims herein, since that antibody does not cross-block binding of 2C4 (see above), nor does it block ligand activation of an ErbB receptor more effectively than huMAb4D5-8.

Thus, aside from the EGFR+ patient subpopulation treated in the claims as discussed above, therapy with an antibody that cross-blocks binding of 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with a humanized 2C4 antibody, is nonobvious over the art.

Turning now to Jardines *et al.*, Applicants submit that this references <u>teaches away</u> from the presently claimed invention.

First, in Jardines *et al.*, col. 2 on page 278, the number of patients who were EGFR-/HER2-, EGFR+/HER2-, or EGFR-/HER2+ (n=170) far exceeded the number of patients who were EGFR+/HER2+ (n=14), so the less common group of HER2+/EGFR+ patients would not be an obvious patient subpopulation to treat.

Moreover, as explained in col. 2 on page 278 of Jardines *et al.*, EGFR+/HER2+ patients had the shortest survival time, in spite of them receiving cancer therapy. This would teach away from the reasonable expectation of success in being able to treat such patients, since they are demonstrably more resistant to treatment.

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In addition, the ability to treat *any* patient subpopulation, let alone a EGFR+/HER2+ subpopulation is not obvious from Jardines *et al.* This is evident from a review of the concluding paragraph on page 279 where the authors say:

> "Further work is clearly necessary to define the effects of EGFR and/or *neu* in the development of mammary adenocarcinomas. If the relationship can be identified, then novel forms of therapy could be developed which would be directed toward the receptors and could possibly involve the use of monoclonal antibodies, mimetics or antisense RNA." (Emphasis in original).

At best, this is an invitation to experiment, rather than guidance concerning therapy that would meet the requirements of 35 USC Section 102/103 prior art.

There is certainly no disclosure or hint in Jardines *et al.* as to cancer therapy with an antibody that cross-blocks binding of 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with a humanized 2C4 antibody.

Turning now to Sliwkowski *et al.*, this paper is concerned with HER2 and HER3, rather than EGFR. While murine MAb 2C4 is mentioned (a humanized form of 2C4 is not described), therapy of an EGFR+ cancer is not. Indeed, this paper provides a biochemical characterization of a HER2-HER3 complex, rather than guidance concerning therapy of human cancer, let alone EGFR+ cancer. Applicants submit that the skilled clinician would not consider Sliwkowski *et al.* to provide either the motivation or reasonable expectation of success for treating EGFR+ cancer, colon, rectal or colorectal cancer, lung cancer, non-small cell lung cancer, or breast cancer.

In Klapper *et al.*, the *in vivo* studies were performed with gastric cancer cells selected due to HER2 overexpression (*e.g.* Fig. 1). Therapy of EGFR+ cancer is not taught, nor is therapy with an antibody that cross-blocks binding of MAb 2C4, or therapy with humanized 2C4. Therapy of colon, rectal or colorectal cancer, lung cancer, non-small cell lung cancer, or breast cancer is not described in this reference either.

Plowman *et al.* concerns assaying a potential agent for activity in inhibition

of signal transduction by a HER2/HER3, HER2/HER4 or HER3/HER4 heterodimer. Therapy of an EGFR+ cancer is not disclosed or suggested, much less therapy with an antibody that cross-blocks binding of MAb 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with humanized 2C4.

Greene *et al.* in the '168 patent is interested in treating a p185-mediated tumor with a peptide that dimerizes with an ErbB protein and that is deficient in tyrosine kinase activity. Therapy of an EGFR+ cancer with an antibody that cross-blocks binding of MAb 2C4, blocks ligand activation of an ErbB receptor more effectively than Herceptin®, or therapy with humanized 2C4 is not disclosed or suggested in Greene.

With respect to claims 24-26, while the Examiner urges that "the ability to establish treatment regimens is well known to those of skill in the art," Applicants point out that administration of the dose about every 3 weeks as in claim 26, in particular, was not obvious at the relevant date. For instance, the approved dosing for the HER2 antibody, Herceptin®, commercially available at the time of filing entailed an initial loading dose of 4 mg/kg, and *weekly* maintenance dose of 2 mg/kg, rather than the less frequent dosing set forth in claim 26 herein.

As to claims 18-19 and 21 concerning therapy with an antibody fragment, such as a Fab, which may be unconjugated, the present application demonstrates the therapeutic utility of such antibody fragments which cross-block 2C4 or block ligand activation of an ErbB receptor (see *e.g.* Figs. 6A-B). While the Examiner relies on Grim *et al.* as allegedly teaching a method of treating lung cancer by administering an antibody fragment, Applicants submit that there is no evidence that the intracellular scFv in Grim can cross-block 2C4 or block ligand activation of an ErbB receptor.

Reconsideration and withdrawal of the Section 103 rejections of claims 1, 2, 4, 7, 16, 17, 20, 24-26, 28, 29, 34 and 60-63, and claims 1, 18, 19 and 21, is respectfully requested.

Obviousness-Type Double Patenting

Claims 1, 2, 4-9, 16-22, 24-27 and 60-63 are provisionally rejected under the

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judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 and 22-31 of copending application 09/602,800 ("the '800 application"). The Examiner contends that the claims of the '800 application are drawn to "methods for treating cancer with an antibody that inhibits ligand activation of an ErbB receptor, and uses the monoclonal antibody 2C4."

Applicants traverse the above rejection. In particular, whereas the claims of the '800 application are actually drawn to methods for treating *prostate* cancer (e.g. androgen dependent prostate cancer, or androgen independent prostate cancer), the claims of the above application concern methods for treating cancer that expresses EGFR and ErbB2; colon, rectal and colorectal cancer; lung cancer (e.g. non-small cell lung cancer); cancer that expresses but does not overexpress ErbB2 receptor; or breast cancer (e.g. metastatic breast cancer). Since the Office has previously held that therapy of different species of cancer are patentably distinct because "Different types of cancers have different mechanisms of action, and require distinct treatment protocols" (Restriction Requirement dated 10/2/01, Paper # 7, page 5), Applicants respectfully request that the provisional obviousness-type double patenting rejection over the '800 application be reconsidered and withdrawn.

Applicants believe that this application is now in condition for allowance, and look forward to early notification to that effect. However, if outstanding issues remain, the Examiner is invited to call the undersigned at the number noted below to discuss same.

Respectfully submitted,
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